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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/673,836	03/29/2001	Triptikumar Mukhopadhyay	085933/0117	5592

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EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 04/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/673,836	MUKHOPADHYAY ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGMENT TO REMARKS/ARGUMENTS AND THE STATUS OF THE CLAIMS

1. The remarks/arguments filed 1/30/04 are acknowledged, entered and considered. Claims 1-4 are now pending in the application. The rejection under 35 U.S.C. 103(a) over the prior art of record is maintained essentially for the same reasons discussed in the previous Office action.

CLAIMS REJECTION-35 U.S.C. § 103(a)

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Balkovec et al., (U.S. Patent No. 5,684,128) taken with Balkovec et al., (U.S. Patent No. 5,159,059).

The instantly claimed invention is directed to a process for converting echinocandin class of peptides (cyclohexapeptidyl lipopeptides) by reducing the C4-htyr (homotyrosine) hydroxyl group of echinocandins to their deoxy analogues by mixing the echinocandin class of peptide with Raney Nickel in a solvent selected from the group consisting of methanol, ethanol and dioxane at a pH 3-9 without protecting and then deprotecting the C5-Orn (ornithine) hydroxyl group prior to reducing the echinocandin class of peptides (i.e., reducing Mulundocandin to Deoxymulundocandin) and then purifying the monodeoxy compound from the crude reaction mixture (claims 1and 2). The process further comprises the reduction of C4-htyr (homotyrosine) hydroxyl group of echinocandins which is carried out by hydrogenolysis with Raney nickel in ethanol at pH 7 and at room temperature and at the ratio of 6.8 ml Raney nickel per millimole of mulundocandin (claims 3 and 4).

Similarly, the prior art of Balkovec et al., ('128 patent) teaches the conversion of cyclohexapeptidyl lipopeptides (echinocandins) to corresponding deoxy analogues under selective reduction by mixing the echinocandin class of peptides with reducing agents such as Raney nickel in solvent such as ethanol, methanol, alcohol, or other ethers at room temperatures with prior protection/deprotection of 3 –hydroxyornithine group prior to reducing the echinocandin class of peptides and then purifying the crude mixtures thereof to obtain the intended compound (see e.g., col. 1, lines 43-55; cols. 3-6; scheme I, cols. 13-17; and claim 1) as directed to claims 1-4. On cols. 13-14, the prior art clearly shows the employment of reducing agent such as Raney nickel in combination with other agents which is useful when the combined reagents is used,

from about 5 to 50 molar equivalents of sodium borohydride and from about 52 to 10 molar equivalents of cobaltous chloride are used for each molar amount of the nitrile. Thus, the prior art teaches the process for conversion of echinocandin class of peptides (Cyclic hexapeptides having a lipophilic side chains) by selective reduction of echinocnadins to their monodeoxy analogues under conditions without prior protection/deprotection of the ornithin hydroxyl group and purification of the monodeoxy compound from the crude reaction mixture, wherein the reduction reaction is carried out by hydrogenolysis from 5 to 50 molar equivalents by using reducing agent such as Raney nickel in combination with other agents at room temperature.

The claims differ by requiring a specific pHs for the conversion of echinocandin class of peptides, i.e., the claims require the use of pH 3-7 and pH 7. However, the primary reference of Balkovec et al., ('128 patent) suggests the use of weakly basic solvents on col. 13, lines 46-50 by stating that the reaction is carried out in a solvent such as dimethylformamide (DMF). Other solvents, which may be employed, include pyridine, collidine and other weakly basic solvents. Thus, clearly suggesting the use of basic solvents. Further, the secondary reference of Balkovec et al., ('059 patent), which teaches a process for producing a compound such as echinocandin or echinocandin-like cyclohexapeptide by selectively reducing said compound in strong acid medium. On Example 10, particularly on col. 23, lines 50-65 teaches the addition of phosphate buffer at pH in the range of 6 to 7 to solubilize the compound with the aid of dimethyl sulfoxide, and later on, adjusting the supernatant to pH 7. Thus, clearly showing the selection of the appropriate process conditions (i.e., pHs) would have been *prima facie* obvious because where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation, *In re Aller*, 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1995).

Therefore, the employment of a process for conversion of echinocandin class of peptides of the formula I (Cyclic hexapeptides having a lipophilic side chains) via single step selective reduction of C4-homotyrosine (C4-htyr) hydroxyl group of echinocnadins to their monodeoxy analogues under neutral conditions (pH 7) without prior protection/deprotection of the equally facile C5-Orn (ornithin) hydroxyl group and purification of the monodeoxy compound from the crude reaction mixture, wherein mulundocandin is converted to deoxymulundocandin and the reduction reaction is carried out by hydrogenolysis with the ratio of 6.8 ml of Raney nickel per millimole of mulundocandin in ethanol at pH 7 and room temperature, appears obvious by the teachings of the prior art and the reasons discussed above, absent of objective factual evidence or unexpected results to the contrary.

ARGUMENTS ARE NOT PERSUASIVE

3. The rejection of claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Balkovec et al., (U.S. Patent No. 5,684,128) taken with Balkovec et al., (U.S. Patent No. 5,159,059).

Applicant's arguments filed 1/30/04 have been fully considered but they are not persuasive. Applicant has argued that the '128 patent does not provide the suggestion or motivation for the conversion of an echinocandin peptide of the monodeoxy analog using Raney nickel. Instead, the '128 patent, at cols. 13 and 14 describes that do not even involve the production of a monodeoxy analog of an echinocandin peptide. Thus, the '128 patent fails to provide the suggestion or motivation for the conversion of an

echinocandin peptide to the monodeoxy analog using Raney nickel, as recited in claim 1 is unpersuasive. Contrary to Applicant's arguments, the Examiner has clearly indicated as discussed above that the '128 patent teaches the conversion of cyclohexapeptidyl lipopeptides (echinocandins) to corresponding deoxy analogues under selective reduction by mixing the echinocandin class of peptides with reducing agents such as Raney nickel in solvent such as ethanol, methanol, alcohol, or other ethers at room temperatures with prior protection/deprotection of 3 –hydroxyornithine group prior to reducing the echinocandin class of peptides and then purifying the crude mixtures thereof to obtain the intended compound (see e.g., col. 1, lines 43-55; cols. 3-6; scheme I, cols. 13-17; and claim 1) as directed to claims 1-4. On cols. 13-14, the prior art clearly shows the employment of reducing agent such as Raney nickel in combination with other agents which is useful when the combined reagents is used, from about 5 to 50 molar equivalents of sodium borohydride and from about 52 to 10 molar equivalents of cobaltous chloride are used for each molar amount of the nitrile. Thus, the prior art teaches the process for conversion of echinocandin class of peptides (Cyclic hexapeptides having a lipophilic side chains) by selective reduction of echinocnadins to their monodeoxy analogues under conditions without prior protection/deprotection of the ornithin hydroxyl group and purification of the monodeoxy compound from the crude reaction mixture, wherein the reduction reaction is carried out by hydrogenolysis from 5 to 50 molar equivalents by using reducing agent such as Raney nickel in combination with other agents at room temperature.

Applicant's assertion that the only reducing agent that is used in all of the examples of the secondary reference of '059 patent is sodium cyanoborohydride and not Raney nickel is noted. However, the primary reference of '128 patent teaches the use of Raney nickel as reducing agent in solvent such as ethanol, methanol, alcohol, or other ethers at room temperatures with prior protection/deprotection of 3 – hydroxyornithine group prior to reducing the echinocandin class of peptides. Thus, the '128 patent teaches the use of Raney nickel as a reducing agent.

With respect to Applicant's allegation that there is no evidence of a suggestion or motivation in the prior art to have modified the teachings of the'128 patent or have combined its teachings with those of the '059 patent, to arrive at the claimed invention is unpersuasive. Contrary to Applicant's allegation, the combined teachings of the prior art clearly motivates one of ordinary skill in the at the time of the invention was made the employment of a process for conversion of echinocandin class of peptides of the formula I (Cyclic hexapeptides having a lipophilic side chains) via single step selective reduction of C4-homotyrosine (C4-htyr) hydroxyl group of echinocnadins to their monodeoxy analogues under neutral conditions (pH 7) without prior protection/deprotection of the equally facile C5-Orn (ornithin) hydroxyl group and purification of the monodeoxy compound from the crude reaction mixture, wherein mulundocandin is converted to deoxymulundocandin and the reduction reaction is carried out by hydrogenolysis with the ratio of 6.8 ml of Raney nickel per millimole of mulundocandin in ethanol at pH 7 and room temperature as discussed above. Therefore, it is made obvious by the combined teachings of the prior art since the

instantly claimed invention which falls within the scope of the combined teachings of the prior art method would have been *prima facie* obvious from said prior art disclosure to a person of ordinary skill in the art because as held in host of cases including *Ex parte Harris*, 748 O.G. 586; *In re Rosselete*, 146 USPQ 183; *In re Burgess*, 149 USPQ 355 and as exemplified by *In re Best*, "the test of obviousness is not express suggestion of the claimed invention in any and all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them".

ACTION IS FINAL

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CONCLUSION AND FUTURE CORRESPONDANCE

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272-0955. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S.F. Low, can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306 for regular communications and (703) 305-7401 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Mohamed/AAM

April 26, 2004

ROBERT A. WAX
PRIMARY EXAMINER